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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/078,531	02/21/2002	Denis Martin	PHARMA-18	3055

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EXAMINER	
SHAHNAN SHAH, KHATOL S	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/078,531	MARTIN ET AL.	
	Examiner	Art Unit	
	Khatol S Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *1-16,22-29 and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-21,30 and 35-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' amendment of August 25, 2004 is acknowledged. Claims 17, 18, 19, 20 have been amended. New claims 35-42 have been added.

2. Claims 1-42 are pending. Claims 1-16, 22-29 and 31-34 are withdrawn from consideration as being drawn to non-elected inventions.

3. Claims 17-21, 30 and 35-42 are under consideration.

Prior Citations of Title 35 Sections

4. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior office action.

Prior Citations of References

5. The references cited or used as prior art in support of one or more rejections in the instant office action have been previously cited and made of record. No form PTO-892 or 1449 has been submitted with this office action.

Objections Withdrawn

6. Objections to the specification made in paragraph 9 of the office action mailed 5/26/2004 is withdrawn in view of applicants' amendments.

7. Objections to the specification made in paragraph 11 of the office action mailed 5/26/2004 is withdrawn in view of applicants' amendments.

8. Objections to claims 19 and 20 made in paragraph 12 of the office action mailed 5/26/2004 is withdrawn in view of applicants' amendments.

Rejections Withdrawn

9. Rejection of claims 17-19, 21 and 30 under 35 U.S.C. 102(b) as being anticipated by Bjorck et al. (WO 99/52939) is withdrawn in view of applicants' amendments.

10. Rejection of claims 17-21 and 30 under 35 U.S.C. 112 second paragraph made in paragraph 18 of the office action mailed 5/26/2004 is withdrawn in view of applicants' amendments.

Objections Maintained

11. Objections to the drawing made in paragraph 8 of the office action mailed 5/26/2004 is maintained. The applicants have not submitted corrected drawings and have requested that this requirement be held in abeyance until subject matter is deemed allowable. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

12. Objections to the specification made in paragraph 10 of the office action mailed 5/26/2004 is maintained. Applicants responded that they will correct the trade marks in due course as requested. The objection will be maintained until such corrections are submitted.

Rejections Maintained

13. Rejection of claims 17-21 and 30 under the judicially created doctrine of obviousness-type double patenting made in paragraph 14 of the office action mailed 5/26/2004 is maintained. No terminal disclaimer has been submitted by the applicants and the conflicting claims in both applications are still pending.

14. Rejection of claims 17-21 and 30 under 35 U.S.C. 112 first paragraph made in paragraph 16 of the office action mailed 5/26/2004 is maintained.

The rejection was as stated below:

Claims 17-21 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising SEQ ID NO: 2, does not reasonably provide enablement for analogs and fragments of a sequence at least 70% identical to SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP) 2164.01(a). Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples (6) the quantity of experimentation, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instant claims are drawn to isolated polypeptides comprising amino acid sequences which are at least 70% identical to SEQ ID NO: 2. Fragments and analogs from these variant sequences are also claimed. These terms can encompass as few as one or more amino acids. Additionally, a fragment or an analog derived from an amino acid sequence which varies by as much as 30% identity from SEQ ID NO: 2 can encompass fragments with nothing in common

with SEQ ID NO: 2 i.e., the fragment or analog could be taken from the 30% of the sequence which is different from SEQ ID NO: 2.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species.

The breadth of the instant claims is drawn to polypeptides, which are not specified in the sequence disclosure. The specification states that substitutions, additions or deletions may be to the defined sequences (see page 9, lines 6-10); however the specification provided no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g. such as various positions or regions directly involved in binding, catalysis in providing the correct three- dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions.

The specification (page 1) recites that these polypeptides may be used to prevent, diagnose and /or treat streptococcal infection. It is unclear how the amino acid sequences are selected or how the skilled artisan would predict the sequences required to accomplish these required functions. The specification does not teach how one would make this selection or teach a method to predetermine the sequence structure for appropriate selection to result in the required affinity constant and antigenic specificity. The art teaches that even minor changes in the amino acid

sequences may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function (see abstract and title). Substitution of amino acids into a known sequence as well as identifying and using fragments of proteins containing an isolated functional domain of a protein is within the realm of protein chemistry and is one of the most unpredictable areas of protein chemistry. For example Burgess et al. (J of Cell Biology, 1990 Vol. 111, pp. 2129-2138) teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Furthermore, Lazar et al (Molecular and Cellular Biology, 1988, Vol. 8, pp. 1247-1252) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

The instant claims are drawn to proteins comprising a sequence with a given percent similarity to a protein. Selective point mutation to one key antigen could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects

of multiple changes in an antigenic determinant could again result in loss of function. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody, which is recognized by the native BVH-P7 protein on the *Streptococcus pyogenes* bacteria, and be ineffective in treating or preventing diseases or conditions caused by infection with *Streptococcus pyogenes*. Applicants have provided no guidance to enable one skilled in the art how to determine, without undue experimentation, the effect of different substitutions and the nature and the extent of the changes that can be made. In view of all of the above, in view of the lack of predictability in the art, and lack of guidance on how to obtain the desired fragments and analogs it is determined that it would require undue experimentation to make and/or use the claimed invention. In summary, the actual invention is not described in such a way that one skilled in the art could grasp the invention and make and/or use the invention and/or reproducibly practice the invention with a reasonable expectation of success, without undue experimentation. In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the invention commensurate in scope with the claims.

Applicants' arguments filed August 25, 2004 have been fully considered but they are not persuasive.

Applicants argue that the specification describes the identification of ten different homologues of the BVH-P7 gene. These homologues show a high degree of sequence identity. For example, figure 3 compares the amino acid sequences from seven different strains of S.

pyogenes. As indicated they are highly conserved, sharing 95% or more sequence identity along their sequenced lengths. See attached Exhibit A.

Applicants further argue the specification provides clear guidance on how to isolate polypeptides that fall within the scope of the claims, and uses this information to successfully identify many different sequences, e.g. illustrated in figure 3.

It is the examiner's position that the specification is not enabled for variant polypeptide sequences or fragments of 10 amino acids in length. It is not clear from the specification what epitopes if any the applicants have specified. The location of protective epitopes has not been identified. Applicants refer to figure 3 has been noted. Figure 3 compares amino acid sequences from different strains of *S. pyogenes,* in contrast *the* instant rejections is targeted towards claimed fragments. The claimed fragments encompasses 10-mer fragments, which can have 5-30% variation from the defined sequences. The fragments could be drawn from the part of the sequence which is completely different from that disclosed in the sequence identifiers. A three amino-acid variation in a 10-mer sequence is quite large and it is unclear what fragments are encompassed by this definition.

Genentech Inc. v. Novo Nordisk NS (CAFC) 42 USPQZd 1001 clearly states:

"Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly

need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. This has not been met with the broad scope of the instant claims, which require invention rather than experimentation. The skilled artisan cannot envision the detailed structure of the encompassed polypeptide fragments, Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate enablement and written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide/fragment itself is required.

With respect to the new claims an isolated polypeptide, which comprises at least one epitope that elicits antibodies specific for S. pyogenes is not enabled. As stated above, the specification is only enabled for an isolated polypeptide comprising SEQ ID NO: 2, does not provide enablement for fragments or immunogenic epitopes.

Conclusion

15. No claims are allowed.

16. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol S Shahnan-Shah whose telephone number is (571)-272-0863. The examiner can normally be reached on 7:30am-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F Smith can be reached on (571)-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Khatol Shahnan-Shah, BS, Pharm, MS

Art Unit 1645,

November 25, 2004

RODNEY P SWARTZ, PH.D
PRIMARY EXAMINER